II. Rejections Under 35 U.S.C. §112, First Paragraph

A. Enablement

Claims 1-40 and 44-79 are rejected as allegedly lacking an enabling disclosure. The basis for the rejection is that "the specification ... does not reasonably provide enablement for the treatment of gram negative bacteria with a potentiator broadly described as acyl hydrazide, oxy amide or 8-hydroxy quinoline." The "support" for the rejection is but one sentence:

> Since the terms acyl hydrazide, oxy amide and 8-hydroxy quinoline encompass such a broad class of compounds, it would take an undue amount of experimentation to determine which specific compounds are useful in the instant invention.

Applicants traverse.

As stated by the CCPA, the Patent Office ***must*** take appellants' specification as in compliance with enablement requirements unless there is reason to doubt "the objective truth" of the specification. Otherwise, there would be no need for appellants to go to the trouble and expense of supporting a "presumptively accurate disclosure." *In re Marzocchi*, 169 UPSQ 370 (CCPA 1971). Here, the examiner has not advanced one shred of evidence in support of the rejection, noting only that the "scope" of applicants' claims is large. This statement – ***the only reason given for the rejection*** – is insufficient to shift the burden to applicants. As such, applicants need to do nothing in response to this improper rejection.

Moreover, this rejection appears to be more directed to utility than to enablement. The examiner has not made any attempt to argue that compounds within the scope of the claims cannot be synthesized, nor that the compounds as class are wholly inadequate to achieve the stated goals of potentiating antibiotic activity and treating bacterial infections. Rather, it would appear that the examiner is arguing that the number of ***potential*** inoperative species somehow

robs the claims of enablement. However, it is not the function of the claims to specifically exclude possible inoperative substances. *Atlas Powder Co. v. E.I. DuPont de Nemours & Co.*, 224 USPQ 409 (Fed. Cir. 1984). And where applicants have limited the scope of the claims to the area where utility has not been properly challenged, maintenance of the rejection is improper. *In re Frillette*, 165 USPQ 259 (CCPA 1970); *In re Buting*, 163 USPQ 689 (CCPA 1969). Thus, even this line of argument goes wanting.

In sum, this is an ungrounded rejection that, even if based upon valid scientific considerations, would fail under the cited legal precedent. Therefore, reconsideration and withdrawal of the rejection is respectfully requested.

B. Written Description

Claims 1-13, 28-40 and 44-77 are rejected as allegedly lacking an adequate description in the specification. The basis for the rejection is that "it is not clear from claim 1 how the bactericidal action of an antibacterial agent is increased when the claim is directed to the administration of an antibiotic potentiator in the absence of a [anti]bacterial agent." Applicants traverse.

First, applicants submit that this rejection is only relevant to claims 1-13, as all of the other claims recite, in addition to a potentiation, an antibacterial agent. Thus, the rejection is improper as to these claims.

Second, with regard to claims 1-9, 12 and 13 (claims 10 and 11 have been canceled), applicants submit that the claim need not recite provision of an antibacterial agent in order to find support in the application. However, in the interest of advancing the prosecution, claim 1 has been amended to recite "A method for increasing the sensitivity of a bacterium to an

antibacterial agent comprising contacting the bacterium with an antibiotic potentiator, wherein said potentiator is an acyl hydrazide or an oxy amide." Clearly, the sensitivity of the bacterium may be increased without the provision of the antibacterial agent.

Reconsideration and withdrawal of the rejection is, therefore, respectfully requested.

III. Rejection Under 35 U.S.C. §102(b) over Abbruzzese *et al.*

Claims 1-13 stand rejected under §102(b) over Abbruzzese *et al.* ("Abbruzzese"). According to the examiner, the reference discloses that 8-hydroxy quinoline has antibacterial activity. Applicants traverse, but in the interest of advancing the prosecution, claim 1 has been amended to exclude 8-hydroxy quinoline, and claims 10 and 11 have been canceled without prejudice or disclaimer. Reconsideration and withdrawal of the rejection is, therefore, respectfully requested.

IV. Rejection Under 35 U.S.C. §103 over Abbruzzese *et al.* and Pfaller *et al.*

Claims 1-40 and 44-79 stand rejected under §103 as obvious over Abbruzzese and Pfaller *et al.* ("Pfaller"). According to the examiner, Abbruzzese teaches that 8-hydroxy quinoline has *in vitro* antibacterial activity, and thus, it would be obvious to combine this compound with any other antibiotic, such as those disclosed by Pfaller. Applicants submit that this rationale cannot support a proper obviousness rejection.

Any obviousness rejection requires that the prior art provide (a) enabling technology, (b) motivation to combine references, as well as (c) a likelihood of success. *In re O'Farrell*, 7 USPQ2d 1673 (Fed. Cir. 1987). Without ***all*** of these elements, no obviousness rejection can stand. Applicants submit that the present rejection fails for at least two of these reasons, namely,

that (i) the prior art is silent as to a motivation to combine any one of the three claimed potentiators – an acyl hydrazide, an oxy amide or an 8-hydroxy quinoline – with an antibiotic, and (ii) that even if combined, there would be no reasonable predictability with regard to the outcome of the combination.

A. Motivation to Combine

First and foremost, the examiner has not made out a *prima facie* case that one of skill in the art, looking at the cited references, would be motivated to combine 8-hydroxy quinoline with a secondary agent. The examiner has pointed to no particular teaching in Abbruzzese that would instruct the skilled artisan to make such a combination with a second antibiotic agent. Similarly, the examiner has not indicated that Pfaller provides anything but a laundry list of individual antibiotics. Thus, applicants submit that there is no showing on the record of a ***clear and definitive suggestion in the cited art that one should make the claimed combination***. Put another way, there are literally millions of potential drug combinations, and the present record is grossly deficient to establish that this particular type of combination should be made.

In re Jones, 21 USPQ2d 1941 (Fed. Cir. 1992) is particularly instructive. This case dealt with the obviousness of a novel salt of the acid known as dicamba. The PTO alleged that prior art, which disclosed a genus encompassing the salt, rendered a claim to that compound obvious. There, the court found the record lacking with regard to motivation when selecting from such a large number of possibilities:

> Conspicuously missing from this record is any ***evidence***, other than the PTO's speculation (if it can be called evidence) that one of skill in the herbicidal art would have been motivated to make the modifications [to] the prior art salts necessary to arrive at the claimed ... salt."

Jones at 1944 (emphasis in original). The court went on to cite *In re Lalu*, 223 USPQ 1257 (Fed. Cir.) for the same proposition. "The prior art must provide one of ordinary skill in the art the motivation to make the proposed molecular modifications needed to arrive at the claimed compound." *Lalu* at 1258.

Thus, the prior art, not the examiner, must provide motivation for this particular species of combination. Here, the record shows no evidence, beyond the mere allegation that antibiotic combinations are known, that would lead one to use the selected potentiators with a antiobiotic. As such, appellants submit that this rejection also suffers from the same defect as described in *Jones* – lack of motivation – and a *prima facie* case can therefore not stand.

B. Likelihood of Success

Despite the examiner's oversimplification of the issues here, applicants submit that it is far from straightforward to predict which drugs should be combined as part of a therapeutic program. To the contrary, scientists have repeatedly established that drug combinations ***are not*** uniformly combinable. Pharmaceutical companies around the world spend ***millions*** of dollars conducting screening assays for suitable drug combinations. In fact, before any combination therapy can be approved for use on humans (or even approved for testing in humans) by the appropriate regulatory authority, it must be shown to be efficacious and safe to use in humans in the relevant animal model/cell culture testing. Certainly, until such testing is completed, no one with approval authority is willing to predict the ultimate usefulness of any given drug combination.

While the combinations that ***do*** turn out to work (*i.e.*, are effective and non-toxic) may seem logical in hindsight, a proper obviousness analysis also requires consideration of the other

combinations which fail, of which there are many. It is only through a hindsight analysis, which the examiner applies here, that one can find the prior art to have suggested both the combination, ***and*** predicted its likely success. *In re Carroll*, 202 USPQ 571 (CCPA 1979) ("One of the more difficult aspects of resolving questions of non-obviousness is the necessity 'to guard against slipping into the use of hindsight.'"), citing *Graham v. John Deere Co.*, 148 USPQ 459 (U.S. Sup. Ct. 1965). As such, the rejection is improper for this second reason, even assuming that a combination of the references cited by the examiner could be advanced.

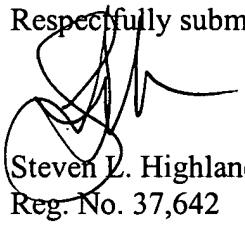
C. Separate Patentability

The examiner has rejected all pending claims as obvious over the cited references. However, applicants point out that no reference has been cited that implicates acyl hydrazides or oxy amides, alone or as a combination therapy. Therefore, the examiner has improperly rejected many of the dependent claims which do not recite 8-hydroxy quinoline, for example, claims 2-9, 15-22, 29-36, or 45-52. Reconsderation and withdrawal of these rejections also is requested.

V. Conclusion

In light of the foregoing, applicants respectfully submit that all claims are in condition for allowance, and an early notification to that effect is earnestly solicited. Should the examiner have any questions, comments or suggestions relating to the referenced patent application, a telephone call to the undersigned is invited.

Respectfully submitted,



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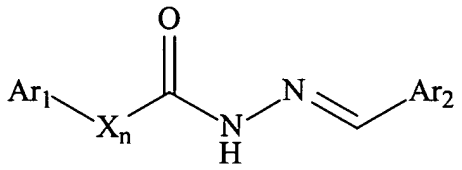
Date: October 22, 2002

APPENDIX A: MARKED UP COPY OF CLAIMS

1. A method for increasing the [bactericidal action of] sensitivity of a bacterium to an antibacterial agent comprising contacting [a] the bacterium with an antibiotic potentiator, wherein said potentiator is an acyl hydrazide[,] or an oxy amide[, or an 8-hydroxy quinoline].

2. The method of claim 1, wherein said acyl hydrazide has the general formula:



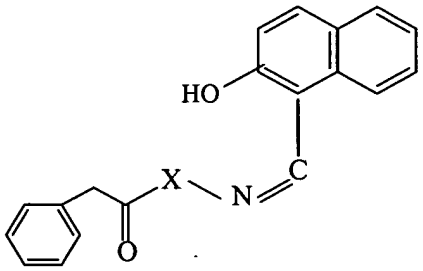
(I)

wherein Ar_1 and Ar_2 are independently aryl, substituted aryl, cycloalkyl, bicycloalkyl, substituted bicycloalkyls, bicycloalkenyl, or substituted bicycloalkenyl, X is CH_2, $C(CH_3)_2$, NH, N-alkyl, N-phenyl, or S and n is 0 or 1.

3. The method of claim 2, wherein Ar_1 is selected from the group consisting of phenyl-, 4-toluoyl-, 4-isopropyl-1-phenyl-, 4-*t*-butyl-1-phenyl-, 2-anisole, 4-ethyl-1-phenyl-, 3-chloro-1-phenyl-, bicyclo[2.2.1]heptane, bicyclo[2.2.1]hept-5-ene, bicyclo[4.1.0]heptane, hexahydro-2,5-methano-pentalene, 1-pyridin-3-yl-, 7,7,-dimethyl-2-oxo-bicyclo[2.2.1]heptane, cylcohexyl-, cycloheptyl- and 4,7,7-trimethyl-3-oxo-2-oxa-bicyclo[2.2.1]heptane.

4. The method of claim 2, wherein Ar_2 is selected from the group consisting of 2-hydroxy-1-naphthyl-, 2-phenol-, 3,5-dichloro-2-phenol-, 4-diethylamino-2-phenol-, 3-methyl-2-phenol-, 4-methyl-2-phenol, 5-methyl-2-phenol, 5-bromo-2-phenol, 5-bromo-3-methoxy-2-phenol, 3-ethoxy-2-phenol- 4,6-dimethoxy-2-phenol-, 4-methoxy-2-phenol and 2-thio-1-phenyl.

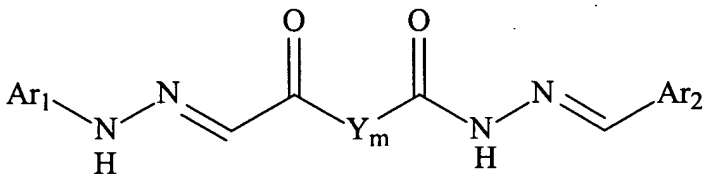
5. The method of claim 1, wherein said acyl hydrazide has the formula:



(II)

wherein X is CH_2, $C(CH_3)_2$, NH, N-alkyl or N-phenyl.

6. The method of claim 1, wherein said acyl hydrazide has the formula:

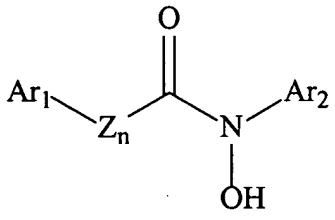


(III)

wherein Ar_1 and Ar_2 are independently aryl or substituted aryls, Y comprises one or more of C, N, and O and m is 1, 2, 3, 4, 5, 6, 7 or 8.

7. The method of claim 6, wherein Ar_1 and Ar_2 are independently selected from the group consisting of 2-hydroxy-1-naphthyl-, 2-phenol-, 3,5-dichloro-2-phenol-, 4-diethylamino-2-phenol-, 3-methyl-2-phenol-, 4-methyl-2-phenol, 5-methyl-2-phenol, 5-bromo-2-phenol, 5-bromo-3-methoxy-2-phenol, 3-ethoxy-2-phenol-, 4,6-dimethoxy-2-phenol-, 4-methoxy-2-phenol and 2-thio-1-phenyl.

8. The method of claim 1, wherein said oxy amide has the formula:

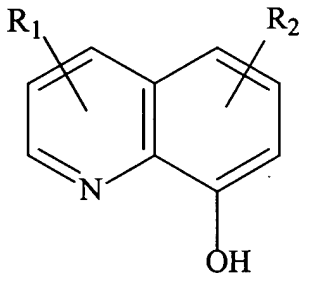


(IV)

wherein Ar_1 and Ar_2 are independently phenyl, naphthyl, toluoyl, anisole, alkylphenyl, alkoxyphenyl, halophenyl, benzyl, or pyridinyl, and Z comprises one or more of C, N, and O, and n=0 or 1.

9. The method of claim 8, wherein Ar_1 is an anisole, n=0, and Ar_2 is a phenyl.

10. (Canceled) The method of claim 1, wherein said 8-hydroxyquinoline has the formula:



(V)

wherein R_1 and R_2 are independently H, alkyl, alkoxy, a halogen, substituted or unsubstituted 1-allylphenyl, benzyl, a hydrazino group (-NHNH2), a substituted hydrazino group, pyrazolyl, alkyl substituted pyrazolyl, an unsubstituted pyridazinyl group, or a substituted pyridazinyl group.

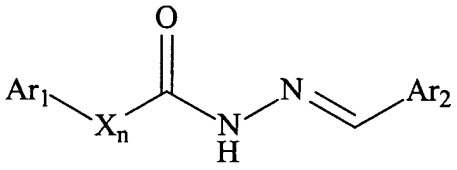
11. (Canceled) The method of claim 10, wherein R_1 is 2-(3,5-dimethyl-pyrazol-1-yl) and R_2 is H.

12. The method of claim 1, wherein said bacterium is of the genus *Staphylococcus, Streptococcus, Enterococcus, Mycobacterium, Listeria, Pseudomonas, Serratia, Escherichia, Klebsiella, Haemophilus, Enterobacter, Proteus, Acinetobacter, Neisseria, Stenotrophomonas, Citrobacter, Salmonella, Morganella Corynebacterium, Pasteurella, Stenotrohonomas, Aeromonas, Bordatella, Providencia, Bacteroides, Shigella, Legionella, Vibrio, Yersinia, Helicobacter, Propionibacterium, Gardnerella* or *Campylobacter.*

13. The method of claim 1, wherein said antibacterial agent is selected from the group consisting of macrolides, ketolides, tetracyclines, chloramphenicols, lincosamides, oxazolidinones, rifamycins, aminoglycosides, glycopeptides, daptomycins, fusidic acids, sulphonamides, cycloserines, β-lactams, diaminopyrimidines, isonicotinic acids, nitrofurans, antiseptics and disinfectants.

14. A method of treating a subject with a bacterial infection comprising administering to said subject an antibacterial agent and an antibiotic potentiator, wherein said potentiator is an acyl hydrazide, an oxy amide, or an 8-hydroxy quinoline.

15. The method of claim 14, wherein said acyl hydrazide has the general formula:



(I)

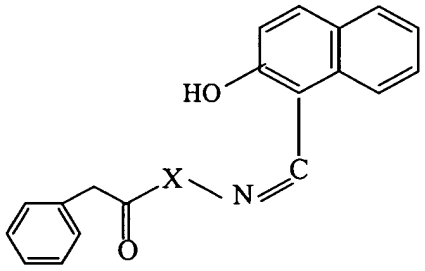
wherein Ar_1 and Ar_2 are independently aryl, substituted aryl, cycloalkyl, bicycloalkyl, substituted bicycloalkyls, bicycloalkenyl, or substituted bicycloalkenyl, X is CH_2, $C(CH_3)_2$, NH, N-alkyl, N-phenyl, or S and n is 0 or 1.

16. The method of claim 15, wherein Ar_1 is selected from the group consisting of phenyl-, 4-toluoyl-, 4-isopropyl-1-phenyl-, 4-*t*-butyl-1-phenyl-, 2-anisole, 4-ethyl-1-phenyl-, 3-chloro-1-phenyl-, bicyclo[2.2.1]heptane, bicyclo[2.2.1]hept-5-ene, bicyclo[4.1.0]heptane, hexahydro-2,5-methano-pentalene, 1-pyridin-3-yl-, 7,7,-dimethyl-2-oxo-bicyclo[2.2.1]heptane, cylcohexyl-, cycloheptyl- and 4,7,7-trimethyl-3-oxo-2-oxa-bicyclo[2.2.1]heptane.

17. The method of claim 15, wherein Ar_2 is selected from the group consisting of 2-hydroxy-1-naphthyl-, 2-phenol-, 3,5-dichloro-2-phenol-, 4-diethylamino-2-phenol-, 3-methyl-2-phenol-, 4-methyl-2-phenol, 5-methyl-2-phenol, 5-bromo-2-phenol, 5-bromo-3-methoxy-

2-phenol, 3-ethoxy-2-phenol- 4,6-dimethoxy-2-phenol-, 4-methoxy-2-phenol and 2-thio-1-phenyl.

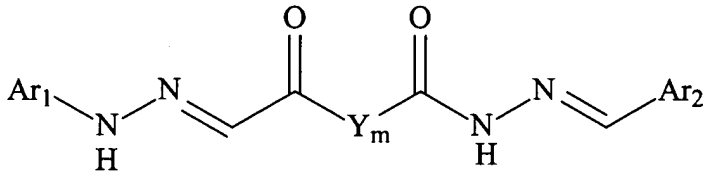
18. The method of claim 14, wherein said acyl hydrazide has the formula:



(II)

wherein X is CH_2, $C(CH_3)_2$, NH, N-alkyl or N-phenyl.

19. The method of claim 14, wherein said acyl hydrazide has the formula:

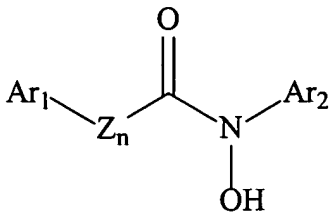


(III)

wherein Ar_1 and Ar_2 are independently aryl or substituted aryls, Y comprises one or more of C, N, and O and m is 1, 2, 3, 4, 5, 6, 7 or 8.

20. The method of claim 19, wherein Ar_1 and Ar_2 are independently selected from the group consisting of 2-hydroxy-1-naphthyl-, 2-phenol-, 3,5-dichloro-2-phenol-, 4-diethylamino-2-phenol-, 3-methyl-2-phenol-, 4-methyl-2-phenol, 5-methyl-2-phenol, 5-bromo-2-phenol, 5-bromo-3-methoxy-2-phenol, 3-ethoxy-2-phenol-, 4,6-dimethoxy-2-phenol-, 4-methoxy-2-phenol and 2-thio-1-phenyl.

21. The method of claim 14, wherein said oxy amide has the formula:

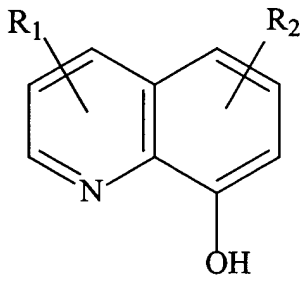


(IV)

wherein Ar_1 and Ar_2 are independently phenyl, naphthyl, toluoyl, anisole, alkylphenyl, alkoxyphenyl, halophenyl, benzyl, or pyridinyl, and Z comprises one or more of C, N, and O, and n=0 or 1.

22. The method of claim 21, wherein Ar_1 is an anisole, n=0, and Ar_2 is a phenyl.

23. The method of claim 14, wherein said 8-hydroxyquinoline has the formula:



(V)

wherein R_1 and R_2 are independently H, alkyl, alkoxy, a halogen, substituted or unsubstituted 1-allylphenyl, benzyl, a hydrazino group (-NHNH2), a substituted hydrazino group, pyrazolyl, alkyl substituted pyrazolyl, an unsubstituted pyridazinyl group, or a substituted pyridazinyl group.

24. The method of claim 23, wherein R_1 is 2-(3,5-dimethyl-pyrazol-1-yl) and R_2 is H.

25. The method of claim 14, wherein said bacterial infection is of the genus *Staphylococcus, Streptococcus, Enterococcus, Mycobacterium, Listeria, Pseudomonas, Serratia, Escherichia, Klebsiella, Haemophilus, Enterobacter, Proteus, Acinetobacter, Neisseria, Stenotrophomonas, Citrobacter, Salmonella, Morganella, Corynebacterium, Pasteurella,*

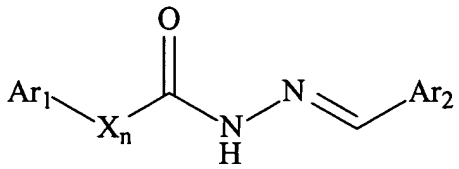
Stenotrohonomas, Aeromonas, Bordatella, Providencia, Bacteroides, Shigella, Legionella, Vibrio, Yersinia, Helicobacter, Propionibacterium, Gardnerella or *Campylobacter.*

26. The method of claim 14, wherein said antibacterial agent is selected from the group consisting of macrolides, ketolides, tetracyclines, chloramphenicols, lincosamides, oxazolidinones, rifamycins, aminoglycosides, glycopeptides, daptomycins, fusidic acids, sulphonamides, cycloserines, β-lactams, diaminopyrimidines, isonicotinic acids, nitrofurans, antiseptics and disinfectants.

27. The method of claim 26, further comprising a first and a second antibacterial agent selected from the group consisting of macrolides, ketolides, tetracyclines, chloramphenicols, lincosamides, oxazolidinones, rifamycins, aminoglycosides, glycopeptides, daptomycins, fusidic acids, sulphonamides, cycloserines, β-lactams, diaminopyrimidines, isonicotinic acids, nitrofurans, antiseptics and disinfectants; wherein said first and said second antibacterial agents are chemically distinct compounds.

28. A bactericidal pharmaceutical composition comprising an antibacterial agent and an antibiotic potentiator, wherein said potentiator is an acyl hydrazide, an oxy amide, or an 8-hydroxy quinoline.

29. The composition of claim 28, wherein said acyl hydrazide has the general formula:



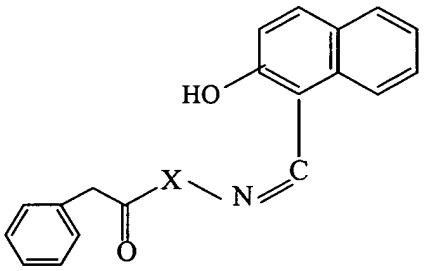
(I)

wherein Ar_1 and Ar_2 are independently aryl, substituted aryl, cycloalkyl, bicycloalkyl, substituted bicycloalkyls, bicycloalkenyl, or substituted bicycloalkenyl, X is CH_2, $C(CH_3)_2$, NH, N-alkyl, N-phenyl, or S and n is 0 or 1.

30. The composition of claim 29, wherein Ar_1 is selected from the group consisting of phenyl-, 4-toluoyl-, 4-isopropyl-1-phenyl-, 4-*t*-butyl-1-phenyl-, 2-anisole, 4-ethyl-1-phenyl-, 3-chloro-1-phenyl-, bicyclo[2.2.1]heptane, bicyclo[2.2.1]hept-5-ene, bicyclo[4.1.0]heptane, hexahydro-2,5-methano-pentalene, 1-pyridin-3-yl-, 7,7,-dimethyl-2-oxo-bicyclo[2.2.1]heptane, cylcohexyl-, cycloheptyl- and 4,7,7-trimethyl-3-oxo-2-oxa-bicyclo[2.2.1]heptane.

31. The composition of claim 29, wherein Ar_2 is selected from the group consisting of 2-hydroxy-1-naphthyl-, 2-phenol-, 3,5-dichloro-2-phenol-, 4-diethylamino-2-phenol-, 3-methyl-2-phenol-, 4-methyl-2-phenol, 5-methyl-2-phenol, 5-bromo-2-phenol, 5-bromo-3-methoxy-2-phenol, 3-ethoxy-2-phenol- 4,6-dimethoxy-2-phenol-, 4-methoxy-2-phenol and 2-thio-1-phenyl.

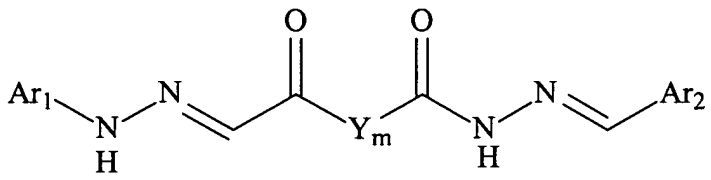
32. The composition of claim 28, wherein said acyl hydrazide has the formula:



(II)

wherein X is CH_2, $C(CH_3)_2$, NH, N-alkyl or N-phenyl.

33. The composition of claim 28, wherein said acyl hydrazide has the formula:

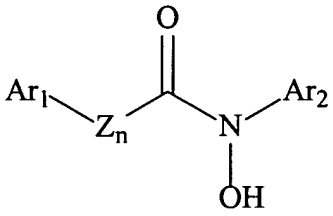


(III)

wherein Ar_1 and Ar_2 are independently aryl or substituted aryls, Y comprises one or more of C, N, and O and m is 1, 2, 3, 4, 5, 6, 7 or 8.

34. The composition of claim 33, wherein Ar_1 and Ar_2 are independently selected from the group consisting of 2-hydroxy-1-naphthyl-, 2-phenol-, 3,5-dichloro-2-phenol-, 4-diethylamino-2-phenol-, 3-methyl-2-phenol-, 4-methyl-2-phenol, 5-methyl-2-phenol, 5-bromo-2-phenol, 5-bromo-3-methoxy-2-phenol, 3-ethoxy-2-phenol-, 4,6-dimethoxy-2-phenol-, 4-methoxy-2-phenol and 2-thio-1-phenyl.

35. The composition of claim 28, wherein said oxy amide has the formula:

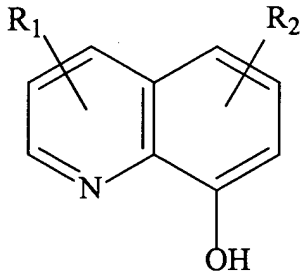


(IV)

wherein Ar_1 and Ar_2 are independently phenyl, naphthyl, toluoyl, anisole, alkylphenyl, alkoxyphenyl, halophenyl, benzyl, or pyridinyl, and Z comprises one or more of C, N, and O, and n=0 or 1.

36. The composition of claim 35, wherein Ar_1 is an anisole, n=0, and Ar_2 is a phenyl.

37. The composition of claim 28, wherein said 8-hydroxyquinoline has the formula:



(V)

wherein R_1 and R_2 are independently H, alkyl, alkoxy, a halogen, substituted or unsubstituted 1-allylphenyl, benzyl, a hydrazino group (-NHNH2), a substituted hydrazino group, pyrazolyl, alkyl substituted pyrazolyl, an unsubstituted pyridazinyl group, or a substituted pyridazinyl group.

38. The composition of claim 37, wherein R_1 is 2-(3,5-dimethyl-pyrazol-1-yl) and R_2 is H.

39. The bactericidal composition of claim 28, wherein said antibacterial agent is selected from the group consisting of macrolides, ketolides, tetracyclines, chloramphenicols, lincosamides, oxazolidinones, rifamycins, aminoglycosides, glycopeptides, daptomycins, fusidic acids, sulphonamides, cycloserines, β-lactams, diaminopyrimidines, isonicotinic acids, nitrofurans, antiseptics and disinfectants.

40. The bactericidal composition of claim 39, further comprising a first and a second antibacterial agent selected from the group consisting of macrolides, ketolides, tetracyclines, chloramphenicols, lincosamides, oxazolidinones, rifamycins, aminoglycosides, glycopeptides, daptomycins, fusidic acids, sulphonamides, cycloserines, β-lactams, diaminopyrimidines, isonicotinic acids, nitrofurans, antiseptics and disinfectants; wherein said first and said second antibacterial agents are chemically distinct compounds.

41. A method of screening for candidate acyl hydrazide antibiotic potentiators, oxy amide antibiotic potentiators or 8-hydroxy quinoline potentiators comprising:

(a) contacting a bacterial cell with an antibacterial agent;
(b) contacting a bacterial cell with said antibacterial agent and an acyl hydrazide, an oxy amide, or an 8-hydroxy quinoline; and
(c) comparing the bactericidal effect of said antibacterial agent in the presence and absence of said acyl hydrazide, oxy amide or 8-hydroxy quinoline,

wherein a decrease in bacterial cell viability indicates said candidate acyl hydrazide, oxy amide or 8-hydroxy quinoline is an antibiotic potentiator.

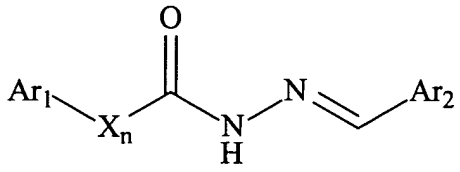
42. The method of claim 41, wherein said antibacterial agent is selected from the group consisting of macrolides, ketolides, tetracyclines, chloramphenicols, lincosamides,

oxazolidinones, rifamycins, aminoglycosides, glycopeptides, daptomycins, fusidic acids, sulphonamides, cycloserines, β-lactams, diaminopyrimidines, isonicotinic acids, nitrofurans, antiseptics and disinfectants.

43. The method of claim 41, wherein said bacterial cell is of the genus *Staphylococcus, Streptococcus, Enterococcus, Mycobacterium, Listeria, Pseudomonas, Serratia, Escherichia, Klebsiella, Haemophilus, Enterobacter, Proteus, Acinetobacter, Neisseria, Stenotrophomonas, Citrobacter, Salmonella, Morganella, Corynebacterium, Pasteurella, Stenotrohonomas, Aeromonas, Bordatella, Providencia, Bacteroides, Shigella, Legionella, Vibrio, Yersinia, Helicobacter, Propionibacterium, Gardnerella* or *Campylobacter.*

44. A method of treating a subject for a bacterial biofilm infection comprising administering to said subject an antibacterial agent and an antibiotic potentiator, wherein said potentiator is an acyl hydrazide, an oxy amide, or an 8-hydroxy quinoline.

45. The method of claim 44, wherein said acyl hydrazide has the general formula:



(I)

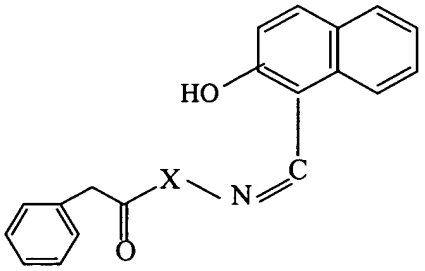
wherein Ar_1 and Ar_2 are independently aryl, substituted aryl, cycloalkyl, bicycloalkyl, substituted bicycloalkyls, bicycloalkenyl, or substituted bicycloalkenyl, X is CH_2, $C(CH_3)_2$, NH, N-alkyl, N-phenyl, or S and n is 0 or 1.

46. The method of claim 45, wherein Ar_1 is selected from the group consisting of phenyl-, 4-toluoyl-, 4-isopropyl-1-phenyl-, 4-*t*-butyl-1-phenyl-, 2-anisole, 4-ethyl-1-phenyl-, 3-chloro-1-phenyl-, bicyclo[2.2.1]heptane, bicyclo[2.2.1]hept-5-ene, bicyclo[4.1.0]heptane, hexahydro-2,5-methano-pentalene, 1-pyridin-3-yl-, 7,7,-dimethyl-2-oxo-

bicyclo[2.2.1]heptane, cylcohexyl-, cycloheptyl- and 4,7,7-trimethyl-3-oxo-2-oxa-bicyclo[2.2.1]heptane.

47. The method of claim 45, wherein Ar_2 is selected from the group consisting of 2-hydroxy-1-naphthyl-, 2-phenol-, 3,5-dichloro-2-phenol-, 4-diethylamino-2-phenol-, 3-methyl-2-phenol-, 4-methyl-2-phenol, 5-methyl-2-phenol, 5-bromo-2-phenol, 5-bromo-3-methoxy-2-phenol, 3-ethoxy-2-phenol- 4,6-dimethoxy-2-phenol-, 4-methoxy-2-phenol and 2-thio-1-phenyl.

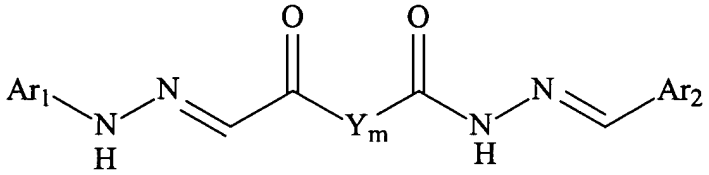
48. The method of claim 44, wherein said acyl hydrazide has the formula:



(II)

wherein X is CH_2, $C(CH_3)_2$, NH, N-alkyl or N-phenyl.

49. The method of claim 44, wherein said acyl hydrazide has the formula:

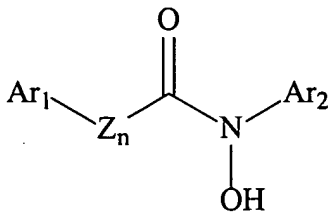


(III)

wherein Ar_1 and Ar_2 are independently aryl or substituted aryls, Y comprises one or more of C, N, and O and m is 1, 2, 3, 4, 5, 6, 7 or 8.

50. The method of claim 49, wherein Ar_1 and Ar_2 are independently selected from the group consisting of 2-hydroxy-1-naphthyl-, 2-phenol-, 3,5-dichloro-2-phenol-, 4-diethylamino-2-phenol-, 3-methyl-2-phenol-, 4-methyl-2-phenol, 5-methyl-2-phenol, 5-bromo-2-phenol, 5-bromo-3-methoxy-2-phenol, 3-ethoxy-2-phenol-, 4,6-dimethoxy-2-phenol-, 4-methoxy-2-phenol and 2-thio-1-phenyl.

51. The method of claim 44, wherein said oxy amide has the formula:

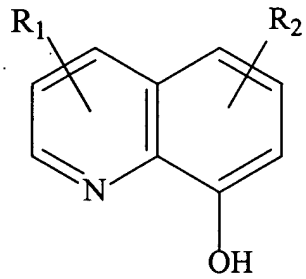


(IV)

wherein Ar_1 and Ar_2 are independently phenyl, naphthyl, toluoyl, anisole, alkylphenyl, alkoxyphenyl, halophenyl, benzyl, or pyridinyl, and Z comprises one or more of C, N, and O, and n=0 or 1.

52. The method of claim 51, wherein Ar_1 is an anisole, n=0, and Ar_2 is a phenyl.

53. The method of claim 44, wherein said 8-hydroxyquinoline has the formula:



(V)

wherein R_1 and R_2 are independently H, alkyl, alkoxy, a halogen, substituted or unsubstituted 1-allylphenyl, benzyl, a hydrazino group (-NHNH2), a substituted hydrazino group, pyrazolyl, alkyl substituted pyrazolyl, an unsubstituted pyridazinyl group, or a substituted pyridazinyl group.

54. The method of claim 53, wherein R_1 is 2-(3,5-dimethyl-pyrazol-1-yl) and R_2 is H.

55. The method of claim 44, wherein said biofilm is of the genus *Staphylococcus, Streptococcus, Enterococcus, Mycobacterium, Listeria, Pseudomonas, Serratia, Escherichia, Klebsiella, Haemophilus, Enterobacter, Proteus, Acinetobacter, Neisseria,*

Stenotrophomonas, Citrobacter, Salmonella, Morganella, Corynebacterium, Pasteurella, Stenotrohonomas, Aeromonas, Bordatella, Providencia, Bacteroides, Shigella, Legionella, Vibrio, Yersinia, Helicobacter, Propionibacterium, Gardnerella or *Campylobacter.*

56. The method of claim 52, wherein said infection is resistant to antibacterial agents.

57. The method of claim 56, wherein said infection is a chronic infection or persistent infection.

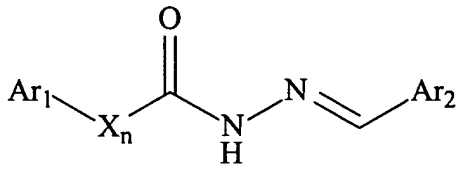
58. The method of claim 54, wherein said infection is endocarditis, osteomyelitis, an infection in a neutropenic subject or a biomaterial infection.

59. The method of claim 44, wherein said antibacterial agent is selected from the group consisting of macrolides, ketolides, tetracyclines, chloramphenicols, lincosamides, oxazolidinones, rifamycins, aminoglycosides, glycopeptides, daptomycins, fusidic acids, sulphonamides, cycloserines, β-lactams, diaminopyrimidines, isonicotinic acids, nitrofurans, antiseptics and disinfectants.

60. The method of claim 59, further comprising a first and a second antibacterial agent selected from the group consisting of macrolides, ketolides, tetracyclines, chloramphenicols, lincosamides, oxazolidinones, rifamycins, aminoglycosides, glycopeptides, daptomycins, fusidic acids, sulphonamides, cycloserines, β-lactams, diaminopyrimidines, isonicotinic acids, nitrofurans, antiseptics and disinfectants; wherein said first and said second antibacterial agents are chemically distinct compounds.

61. A pharmaceutical composition for inhibiting bacterial biofilm viability comprising an antibacterial agent and an antibiotic potentiator, wherein said potentiator is an acyl hydrazide, an oxy amide, or an 8-hydroxy quinoline.

62. The composition of claim 61, wherein said acyl hydrazide has the general formula:



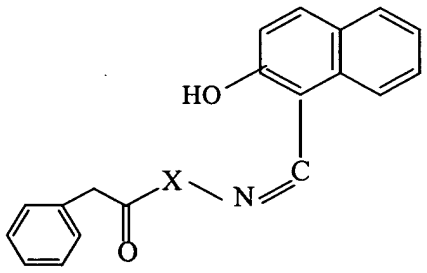
(I)

wherein Ar_1 and Ar_2 are independently aryl, substituted aryl, cycloalkyl, bicycloalkyl, substituted bicycloalkyls, bicycloalkenyl, or substituted bicycloalkenyl, X is CH_2, $C(CH_3)_2$, NH, N-alkyl, N-phenyl, or S and n is 0 or 1.

63. The composition of claim 62, wherein Ar_1 is selected from the group consisting of phenyl-, 4-toluoyl-, 4-isopropyl-1-phenyl-, 4-*t*-butyl-1-phenyl-, 2-anisole, 4-ethyl-1-phenyl-, 3-chloro-1-phenyl-, bicyclo[2.2.1]heptane, bicyclo[2.2.1]hept-5-ene, bicyclo[4.1.0]heptane, hexahydro-2,5-methano-pentalene, 1-pyridin-3-yl-, 7,7,-dimethyl-2-oxo-bicyclo[2.2.1]heptane, cylcohexyl-, cycloheptyl- and 4,7,7-trimethyl-3-oxo-2-oxa-bicyclo[2.2.1]heptane.

64. The composition of claim 62, wherein Ar_2 is selected from the group consisting of 2-hydroxy-1-naphthyl-, 2-phenol-, 3,5-dichloro-2-phenol-, 4-diethylamino-2-phenol-, 3-methyl-2-phenol-, 4-methyl-2-phenol, 5-methyl-2-phenol, 5-bromo-2-phenol, 5-bromo-3-methoxy-2-phenol, 3-ethoxy-2-phenol- 4,6-dimethoxy-2-phenol-, 4-methoxy-2-phenol and 2-thio-1-phenyl.

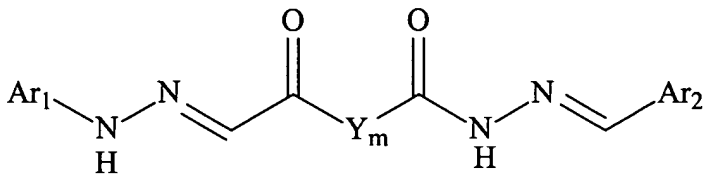
65. The composition of claim 61, wherein said acyl hydrazide has the formula:



(II)

wherein X is CH_2, $C(CH_3)_2$, NH, N-alkyl or N-phenyl.

66. The composition of claim 61, wherein said acyl hydrazide has the formula:

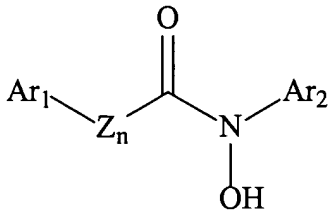


(III)

wherein Ar_1 and Ar_2 are independently aryl or substituted aryls, Y comprises one or more of C, N, and O and m is 1, 2, 3, 4, 5, 6, 7 or 8.

67. The composition of claim 66, wherein Ar_1 and Ar_2 are independently selected from the group consisting of 2-hydroxy-1-naphthyl-, 2-phenol-, 3,5-dichloro-2-phenol-, 4-diethylamino-2-phenol-, 3-methyl-2-phenol-, 4-methyl-2-phenol, 5-methyl-2-phenol, 5-bromo-2-phenol, 5-bromo-3-methoxy-2-phenol, 3-ethoxy-2-phenol-, 4,6-dimethoxy-2-phenol-, 4-methoxy-2-phenol and 2-thio-1-phenyl.

68. The composition of claim 61, wherein said oxy amide has the formula:

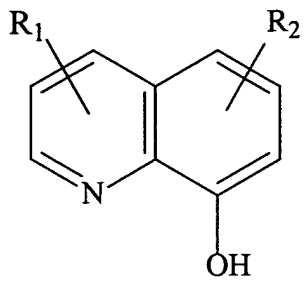


(IV)

wherein Ar_1 and Ar_2 are independently phenyl, naphthyl, toluoyl, anisole, alkylphenyl, alkoxyphenyl, halophenyl, benzyl, or pyridinyl, and Z comprises one or more of C, N, and O, and n=0 or 1.

69. The composition of claim 68, wherein Ar_1 is an anisole, n=0, and Ar_2 is a phenyl.

70. The composition of claim 61, wherein said 8-hydroxyquinoline has the formula:



(V)

wherein R_1 and R_2 are independently H, alkyl, alkoxy, a halogen, substituted or unsubstituted 1-allylphenyl, benzyl, a hydrazino group (-NHNH2), a substituted hydrazino group, pyrazolyl, alkyl substituted pyrazolyl, an unsubstituted pyridazinyl group, or a substituted pyridazinyl group.

71. The composition of claim 70, wherein R_1 is 2-(3,5-dimethyl-pyrazol-1-yl) and R_2 is H.

72. The composition of claim 61, wherein said biofilm is of the genus *Staphylococcus, Streptococcus, Enterococcus, Mycobacterium, Listeria, Pseudomonas, Serratia, Escherichia, Klebsiella, Haemophilus, Enterobacter, Proteus, Acinetobacter, Neisseria, Stenotrophomonas, Citrobacter, Salmonella, Morganella, Corynebacterium, Pasteurella, Stenotrohonomas, Aeromonas, Bordatella, Providencia, Bacteroides, Shigella, Legionella, Vibrio, Yersinia, Helicobacter, Propionibacterium, Gardnerella* or *Campylobacter.*

73. The composition of claim 61, wherein said infection is resistant to antibacterial agent agents.

74. The composition of claim 73, wherein said infection is a chronic infection or persistent infection.

75. The composition of claim 74, wherein said infection is endocarditis, osteomyelitis, an infection in a neutropenic subject or a biomaterial infection.

76. The composition of claim 61, wherein said antibacterial agent is selected from the group consisting of macrolides, ketolides, tetracyclines, chloramphenicols, lincosamides, oxazolidinones, rifamycins, aminoglycosides, glycopeptides, daptomycins, fusidic acids, sulphonamides, cycloserines, β-lactams, diaminopyrimidines, isonicotinic acids, nitrofurans, antiseptics and disinfectants.

77. The composition of claim 76, further comprising a first and a second antibacterial agent selected from the group consisting of macrolides, ketolides, tetracyclines, chloramphenicols, lincosamides, oxazolidinones, rifamycins, aminoglycosides, glycopeptides, daptomycins, fusidic acids, sulphonamides, cycloserines, β-lactams, diaminopyrimidines, isonicotinic acids, nitrofurans, antiseptics and disinfectants; wherein said first and said second antibacterial agents are chemically distinct compounds.

78. A method for increasing the bactericidal action of an antibacterial agent comprising:

(a) contacting a bacterial cell with an antibacterial agent; and

(b) contacting said bacterial cell with an acyl hydrazide potentiator, an oxy amide potentiator, or an 8-hydroxy quinoline potentiator,

wherein said potentiator promotes the intracellular accumulation of a metal.

79. The method of claim 78, wherein said metal is iron, copper or manganese.